Syndrome — a changing concept*

By Stanley Jablonski†

8603 Virginia Avenue
Annandale, Virginia 22003

Syndrome is one of the oldest terms in the medical vocabulary. Traditionally, the term has been used mainly as a designation for complex medical entities, such as multiple abnormalities, that are characterized by clusters of concurring symptoms, usually three or more. During the mid-twentieth century, the meaning and the use of the term were altered. First to take place was an attempt to eliminate physicians' names from syndrome nomenclature, resulting in a significant increase in the use of descriptive designations in proportion to eponyms. But the trend was counterbalanced by the creation of new classes of eponyms. Eponymous syndrome nomenclature now includes the names of literary characters, patients' surnames, subjects of famous paintings, famous persons, geographic locations, institutions, biblical figures, and mythological characters. This was followed by a relaxation in the scope of the definition of syndrome, wherein the term could also be used as a modifier indicating a special (sometimes unspecified) complexity of an already named pathological condition. Eventually *syndrome* changed from its original use as an exclusively medical term and came to mean anything unusual, abnormal, bizarre, or humorous, whether medical, social, behavioral, or cultural. This unrestrained use of the term is the principal cause of an enormous volume of the sometimes irrelevant syndrome literature cluttering databases in the MEDLARS system and of the deterioration of "SYNDROME" as a specific MeSH term and a useful search parameter.

INTRODUCTION

Syndrome has been used as a designation for disorders that were marked by etiologically nonspecific similar groups of manifestations. The use of the term remained reasonably constant for more than two millennia until the mid-twentieth century when its scope was expanded to also include all morbid conditions characterized by complex symptomatology, to the point that almost any pathological condition may be now designated as a syndrome. Indexers and searchers of medical literature are thus faced with the situation where some writers continue to use the term in the traditional manner, restricting it to congenital disorders involving multiple organs or systems, while others consider it a nonspecific modifier denoting special complexity of already named entities or even as an expression of humor. The value of *syndrome* as a specific subject heading or a search parameter has been severely compromised. The purpose of this paper is to review the current use of *syndrome* with special emphasis on indexing and searching problems resulting from inconsistencies and imprecise use of the term.

HISTORY

The term *syndrome* (from the Greek *syndrome* 'concurrence') traditionally was defined as a pathological condition associated with a cluster of co-occurring symptoms, usually three or more. It was often used provisionally with the expectation that once the nature of the condition was clarified, a more precise designation would take its place. It is one of the oldest as well as most frequently used and misused words in modern medical vocabulary.

The meaning of *syndrome* remained very much unchanged from the time of Hippocrates until well into the seventeenth century, when Thomas Sydenham concluded that *syndrome* and *disease* were synonyms

* History and nomenclature of the term *syndrome* were discussed more extensively in a previous article: Jablonski S. Syndrome: le mot de jour. Am J Med Genet Jun;39(3):342–6.

† Formerly head of indexing, National Library of Medicine, Bethesda, Maryland.

and the former practically vanished from the literature for almost two centuries as a superfluous designation. Rediscovery of the term took place by the end of the nineteenth century when it became apparent that existing methods for naming pathological conditions by combining the names of the affected organs with appropriate prefixes and suffixes were inadequate when dealing with complex disorders, such as multiple abnormalities, errors of metabolism, and multisystem or multiorgan disorders. Mainly because their complexity defied simple descriptive designations, and partly in an attempt to give appropriate credit to those who were first to have described them, many syndromes were given eponymous names [1].

This is not to say that the acceptance of *syndrome* by the twentieth-century physicians was universal. The lack of enthusiasm for the term is well reflected in the *Index-Catalogue of the Library of the Surgeon General's Office,* which in the first series (1893) did not even recognize the concept [2]. In the second series (1912), there were only five citations under the heading SYNDROME [3]. All syndrome entries were cross-referenced to nonsyndromic headings in the third series (1932) [4]. Similarly, the first Dorland's edition of *The American Medical Dictionary* (1900) listed only thirty-two syndromes [5]. However, in time, *syndrome* gradually became an accepted term, particularly useful in naming newly described entities characterized by seemingly unrelated multiple symptoms that occur in clusters.

In the mid-twentieth century, several events drastically altered the meaning and use of the term. The excessive accumulation of syndromes under the names of certain physicians, the difficulty in differentiating syndromes named after different individuals with the same surnames, and the contention that descriptive terms are superior to eponyms, were some of the examples. Editors of some leading journals campaigned to replace the custom of naming syndromes after the physicians, who were said to have originally described them, with descriptive designations. The majority of anti-eponym arguments were well founded. There are, for instance, more than fifteen eponymous designations credited to Fanconi, and there are at least thirteen Smiths who independently described different and completely unrelated syndromes, thus rendering the eponyms *Fanconi's syndrome* and *Smith's syndrome* practically useless [6]. The use of the possessive form in already existing eponymous names has also been criticized, and it has been suggested that the nominative form is more appropriate.

CURRENT USE OF THE TERM

The attempt to replace eponyms with descriptive syndrome names has resulted in a significant drop in the number of new syndromes named after physicians, but the effort has been counterbalanced by the creation of new classes of eponyms, whereby just about any proper name is a potential candidate for an eponymous syndrome designation: for example, patients' surnames (either in full or abbreviated, as in Johnie McL syndrome, G syndrome, or Christmas syndrome); subjects of paintings (Mona Lisa syndrome); famous persons (Lou Gehrig syndrome); geographic locations (Tangier syndrome); institutions (Floating Harbor syndrome); and biblical (Job syndrome), historical (Diogenes syndrome), and literary (Rip Van Winkle syndrome) characters [6].

Most authors were successful, however, in providing newly observed syndromes with appropriate descriptive names, such as the ataxia-telangiectasia syndrome, oto-palato-digital syndrome, acquired immunodeficiency syndrome (AIDS), and the like. Those syndromes that were too complex or contained too many elements to be incorporated into designations of a manageable length were identified by sometimes imaginative initialisms and acronyms, such as the Lentigines-Electrocardiographic abnormalities-Ocular hypertelorism-Pulmonary stenosis-Abnormalities of genitalia-Retardation of growth-sensorineural Deafness syndrome (LEOPARD syndrome).

Nevertheless, some entities, such as polymorphonuclear leukocyte dysfunction due to absence of membrane glycoprotein deficiency, defy the ability of authors to create concise syndromic designation. These remain unnamed, as shown in McKusick's *Mendelian Inheritance in Man* [7]. Before the custom of naming syndromes after physicians went out of style, all these difficult-to-name disorders probably would have been given eponymous designations.

Broadening the meaning of *syndrome* was another step in the evolution of the term, and this had the most profound influence on how it is now used. Its initially narrow definition (a condition characterized by a specific set of symptoms) was expanded to serve as a designator of special, sometimes undefined, complexity (syndromic properties?) of already named diseases, wherein well-known conditions, such as malaria and tuberculosis, became the malaria syndrome and tuberculosis syndrome, respectively. The practice, initially observed mainly in the postwar Russian literature, gradually came to be used in most medical publications worldwide. In a further broadening of its scope, *syndrome* is now often also used as a synonym for a wide variety of terms, including disease, symptom complex, sign, manifestation, and association.

Once used only to denote individual entities, *syndrome* is now frequently also applied as a heading for groups of similar or related conditions; for example, myelodysplastic syndrome represents a broad class of cytopenias, and the headache syndrome is not a syn-

drome in its customary sense but rather a large group of neurological conditions involving the head, neck, and throat, having otherwise little in common. Eventually, *syndrome* emerged from its traditional role as an exclusively medical term to become an all-purpose word used to denote anything bizarre, out-of-the-ordinary, or humorous, whether medical, behavioral, social, or cultural. In its current use, the term is much like Proteus, a mythological Greek god known for his ability to assume different forms, and thus is undefined and probably undefinable, presenting a different face any time one confronts it and meaning whatever one wishes it to mean.

There is no single definition that adequately reflects all the variations in the use of *syndrome* [8]. One that is generally followed by dysmorphologists and geneticists, who are the principal users of the term, states that it is "an etiologically defined entity of unknown pathogenesis not to be confused with 'disease symptom complex,' or 'sequence,' pertaining to only those conditions which are characterized by clusters of identical or similar symptoms" [9–10]. In other fields, the term is used differently, its definition and scope being adapted to the needs of individual authors.

One of the immediate consequences of this unrestrained use of the term is an enormous growth of the literature in which the word *syndrome* is used—from only five citations in the second series of the *Index-Catalogue* in 1912 [11], as mentioned earlier, to more than 1,500 articles that were added each month to the MEDLARS database in 1991. And similarly, the first edition of Dorland's dictionary had only 12 entries in 1900 [12], whereas the 1991 edition of Jablonski's dictionary included more than 15,000 syndrome names [13].

INDEXING AND SEARCHING PROBLEMS

To the indexer, *syndrome* presents a particularly troublesome concept. When indexing, the first problem to resolve is that of differentiation of legitimate syndromes from those in which the term is used imprecisely, facetiously, or as an expression of humor. *The old doctor syndrome, oh my aching back syndrome,* and *the pregnant virgin syndrome* are readily recognizable as nonsyndromic entities that more appropriately would be indexed under the heading "WIT AND HUMOR." Similarly, the hypertension syndrome and tuberculosis syndrome are indexed adequately only under "HYPERTENSION" and "TUBERCULOSIS, PULMONARY," without the need for coordination under "SYNDROME."

Somewhat more involved are the situations in which *syndrome* is used as a synonym for other terms. For instance, are the entities the moyamoya, or Kawakita, syndrome (angiographic manifestations of some cerebrovascular disorders), Clerc-Lévy-Cristesco syndrome (electrocardiographic manifestations of paroxysmal tachycardia), and Swyer-James syndrome (abnormal transradiacency of one lung) actually syndromes, or is the term *syndrome* merely used as a synonym for *manifestations*?

Legitimate syndromes that are represented in MeSH [14] by nonsyndromic subject headings are also indexed without the coordinate heading "SYNDROME," e.g., the von Gierke syndrome is indexed only under "GLYCOGEN STORAGE DISEASE, TYPE I," and trisomy syndromes go only under "TRISOMY" and appropriate chromosome headings, and not also under "SYNDROME."

Multiple eponyms present another difficult area. There are two unrelated Forestier syndromes: the Forestier syndrome I, which is indexed under "POLYMYALGIA RHEUMATICA," and the Forestier syndrome II, which is indexed under "HYPEROSTOSIS, DIFFUSE, IDIOPATHIC SKELETAL." The literature seldom identifies the specific type. In a similar category are the multiple eponyms named after different persons. The Sjögren's syndrome (a MeSH term) originally reported by Henrik Samuel Sjögren, which is characterized by dryness of the mouth and eyes, enlarged salivary glands, and gastritis, may be confused with the one described by Karl Gustaft Torsten Sjögren. This latter syndrome is characterized by ichthyosis, erythroderma, and mental retardation and is indexed under "ICHTHYOSIFORM ERYTHRODERMA, CONGENITAL." In another example, the Munchausen syndrome by proxy is actually a form of child abuse and is not the same entity as the Munchausen syndrome [15].

Differentiation of syndromes with overlapping phenotypes presents still another difficult problem. The Jaffe-Lichtenstein syndrome, for example, when occurring in association with skin pigmentation and sexual precocity, is considered to be a different entity that is known as the McCune-Albright syndrome, and the Jadassohn-Lewandowski syndrome with leukosis is another name for the Jackson-Lawler syndrome.

There are now in the literature some 20,000 entities that at one time or another have been referred to as syndromes, some of which are well known and frequently written about, many having accumulated thousands of references. At the other end of the spectrum, many syndromes appear in the literature infrequently, sometimes once or twice, never to be heard of again.

The controlled format of MeSH vocabulary can accommodate only those syndromes that are of primary importance and appear in the literature with a reasonable frequency. There are now 366 syndromes in MeSH represented by specific subject headings, and several hundred additional syndromic entities which are indexed under specific nonsyndromic headings

[16]. Those syndromes not represented in MeSH are indexed in accordance with rules that are spelled out in the *MEDLARS Indexing Manual*:

> Index under the dominant features of the syndrome as described by the author and as discussed in the text. In general, do not use more than three diseases in the syndrome constellation. Add the heading SYNDROME [17].

These indexing rules are reasonable and probably the best ones that can be devised under the constraints of the complexity and size of the MEDLARS database and without overwhelming the system with a huge volume of additional data. But, as with everything in life, the procedure is not perfect.

The task of identifying the dominant features of a syndrome is not always a simple one. The phenotypes of many syndromes, especially those pertaining to multiple abnormalities, may consist of a large number of elements (sometimes more than fifty) that are frequently arranged in different orders of importance to reflect authors' own specialties, areas of interest, and prejudices, thus making it extremely difficult to identify the dominant feature of a syndrome with any degree of consistency. In an attempt to standardize the indexing of syndromes, the 1974 edition of the *Integrated Authority File*, an internal indexing aid of the Index Section of the National Library of Medicine (NLM), was provided with fixed sets of subject headings for syndromes not listed in MeSH [18]. The indexing aid was helpful to the indexers and searchers in that it provided instructions that could be also used as parameters in search formulations for individual syndromes. But its usefulness was limited to only those who had a direct access to indexing aids. Moreover, the maintenance of such an aid proved to be too costly in time and personnel to justify its continuation.

Many problems experienced by the indexers are shared by the searchers. The profusion of synonyms is one of these problems. Jablonski's dictionary has more than 15,000 syndrome names, of which slightly more than 5,000 are main terms and the remaining 10,000 represent the synonyms. There are an average of three synonyms per syndrome, some entities having as many as fifty different names [19]. There is no universally accepted preferred terminology in syndrome nomenclature; the choice of names varies with editorial policies of individual journals, specialties, languages, and nationalities of publications. A condition known in the United States as the Beckwith syndrome is referred to in Europe as the Wiedemann syndrome, and the editors of journals with strong anti-eponym policies use for the same conditions names such as the exophthalmos-macroglossia-gigantism (EMG) syndrome, familial macroglossia omphalocele syndrome, or macroglossia-omphalocele-visceromegaly syndrome. In this instance, MeSH editors solved the problem neatly by combining the two eponymic versions into a single heading, "BECKWITH-WIEDEMANN SYNDROME." Other syndromes defy simple solutions. The Uehlinger syndrome, as an example, may appear in the literature as the Roy syndrome, Roy-Jutras syndrome, Touraine-Solente-Gole' (TSG) syndrome, bulldog scalp, megalia ossium et cutis, washboard scalp, and some thirty other synonyms. It is up to the indexer to sort out the synonyms and determine that this condition is indexed under the heading "OSTEOARTHROPATHY, PRIMARY HYPERTROPIC," so that the searcher can find it there, no matter what name is used in the literature.

However, searchers have some advantage over indexers in that they can access specific concepts in the literature through the use of the text word search technique. The Gorlin-Chaudhry-Moss syndrome (craniosynostosis, midface hypoplasia, hypertrichosis, and anomalies of the heart, eyes, teeth and external genitalia) is indexed in most instances under the headings "ABNORMALITIES, MULTIPLE," "CRANIOSYNOSTOSIS," "FACE/abnormalities," "HYPERTRICHOSIS," and "SYNDROME," except for situations in which other aspects of the phenotype may be identified as the most important, thus requiring a different approach in indexing. But the searcher can bypass the indexing and go directly to the term Gorlin-Chaudhry-Moss syndrome.

A fairly new but rapidly expanding practice is that of naming syndromes by appending "pseudo-" and "-like" to the names of already known and well-documented syndromes with similar phenotypes, even though they represent separate entities with entirely different etiologies. The pseudo-Addison (or Addison-like) syndrome is a form of salt-losing nephropathy which should not be confused with the Addison syndrome, and the thalidomide-like syndrome, which is characterized by symptoms similar to those in the thalidomide syndrome, has nothing to do with thalidomide-induced embryopathy, and thus is indexed and must be searched differently.

In the same category are the "reverse" syndromes. The reverse Sjögren (or Creyx-Lévy) syndrome differs from the Sjögren syndrome in that dryness of the mouth is replaced by hypersecretion, thus being an entirely different entity.

Other syndromes that may require some thought on the part of a searcher are those with overlapping phenotypes. As an example, the symptoms of the Harada syndrome overlap those of the Vogt-Koyanagi syndrome, and the Heiderlhain syndrome is considered by some to be analogous to the Nevin syndrome, both conditions being variants of the Jakob-Creutzfeld syndrome.

These are some examples of problems faced by in-

dexers and searchers who are involved with the syndrome nomenclature. They are presented and discussed, not because neat solutions are at hand, but because those who work daily with the literature should constantly be aware of the intricacies and complexities of the terms that make it up. We have witnessed an enormous evolution in information technology during the past three decades, but intelligence, experience, ingenuity, and familiarity with the subject matter are still the most important weapons in the arsenal of the medical bibliographer.

ACKNOWLEDGMENTS

I would like to express my appreciation to members of the staff of NLM for their generous assistance in the preparation of this article. I am especially indebted to Eve Marie Lacroix, Karen Patrias, Kristine Scannell, Robert Mehnert, Peri Schuyler, Dr. Nancy Wright, Mary Hantzes, Dr. Maria Farkas, Atsuko Craft, and Mina Smith.

REFERENCES

1. JABLONSKI S. Syndrome: le mot de jour. Am J Med Genet 1991 Jun;39(3):342–6.
2. Index-catalogue of the Library of the Surgeon-General's Office, United States Army. 1st Series, v.14. Washington, DC: Government Printing Office, 1893.
3. Index-catalogue of the Library of the Surgeon-General's Office, United States Army. 2d Series, v.17. Washington, DC: Government Printing Office, 1912.
4. Index-catalogue of the Library of the Surgeon-General's Office, United States Army. 3d Series, v.10. Washington, DC: Government Printing Office, 1932.
5. DORLAND W. The American medical dictionary. 1st ed. Philadelphia: Saunders, 1900.
6. JABLONSKI S. Dictionary of syndromes and eponymic diseases. 2d ed. Malabar, FL: Krieger, 1991.
7. MCKUSICK VA. Mendelian inheritance in man. 7th ed. Baltimore: John Hopkins University Press, 1986.
8. JABLONSKI, Syndrome, op. cit.
9. SPRANGER JW. Krankheit, syndrom, sequenz. Monatschr Kinderheilkd 1989;137:2–7.
10. SPRANGER J, BENIRSCHKE K, HALL JG, LENZ W ET AL. Errors in morphogenesis. Concepts and terms. Recommendations of an International Working Group. J Pediat 1982;100:160–5.
11. Index-catalogue, 2d series, op. cit.
12. DORLAND, op. cit.
13. JABLONSKI, Dictionary, op. cit.
14. NATIONAL LIBRARY OF MEDICINE. Medical subject headings—annotated alphabetic list. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, 1991.
15. JABLONSKI, Dictionary, op. cit.
16. NATIONAL LIBRARY OF MEDICINE, op. cit.
17. NATIONAL LIBRARY OF MEDICINE. MEDLARS indexing manual. Bethesda, MD: U.S. Department of Health, Education and Welfare, National Institutes of Health, 1976.
18. NATIONAL LIBRARY OF MEDICINE. Integrated authority file. Bethesda, MD: U.S. Department of Health, Education and Welfare, National Institutes of Health, 1974.
19. JABLONSKI, Dictionary, op. cit.

Received October 1991; accepted May 1992